

ABSTRACT

A DNA fragment distinct from the epidermal growth factor receptor (EGFR) and *erbB-2* genes was detected by reduced stringency hybridization of *v-erbB* to normal genomic human DNA. Characterization of the cloned DNA fragment mapped the region of *v-erbB* homology to three exons with closest homology of 64% and 67% to a contiguous region within the tyrosine kinase domains of the EGFR and *erbB-2* proteins, respectively. cDNA cloning revealed a predicted 148 kd transmembrane polypeptide with structural features identifying it as a member of the *erbB* family, prompting designation of the new gene as *erbB-3*. It was mapped to human chromosome 12q11–13 and was shown to be expressed as a 6.2 kb transcript in a variety of normal tissues of epithelial origin. Markedly elevated *erbB-3* mRNA levels were demonstrated in certain human mammary tumor cell lines. These findings indicate that increased *erbB-3* expression, as in the case of EGFR and *erbB-2*, plays a role in some human malignancies. Using *erbB-3* specific antibodies (polyclonal or monoclonal), the *erbB-3* protein was identified as a 180 kDa glycoprotein, gp180^{*erbB-3*}. The intrinsic catalytic function of gp180^{*erbB-3*} was uncovered by its ability to autophosphorylate *in vitro*. Ligand-dependent signaling of its cytoplasmic domain was established employing transfectants which express a chimeric EGFR/*erbB-3* protein, gp180^{EGFR/*erbB-3*}. EGF induced tyrosine phosphorylation of the chimera and promoted soft agar colony formation of such transfectants. These findings, combined with the detection of constitutive tyrosine phosphorylation of gp180^{*erbB-3*} in 4 out of 12 human mammary tumor cell lines, implicate the activated *erbB-3* product in the pathogenesis of some human malignancies. Thus, this invention also relates to a method for detecting a receptor ligand capable of either activating or down-regulating the receptor protein, as well as procedures for purifying the resultant ligand; a method of screening potential ligand analogs for their ability to activate the receptor protein; and procedures for targeting a therapeutic drug to cells having a high level of the receptor protein.